3781
N53M

The Condensation of Certain Methylketones with Isatin by the Knoevenagel Method

---

THIS THESIS HAS BEEN ACCEPTED BY THE GRADUATE SCHOOL OF NEW YORK UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

JUNE, 1932

BY

J. SCOTT MACLENNAN

STANFORD UNIVERSITY LIBRARIES
WITHDRAWN

[Reprinted from the Journal of the American Chemical Society, Vol. 54, 4739 (1932).]

The Condensation of Certain Methylketones with Isatin by the Knoevenagel Method

THIS THESIS HAS BEEN ACCEPTED BY THE GRADUATE SCHOOL OF NEW YORK UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

JUNE, 1932

BY

J. SCOTT MACLENNAN

[Reprinted from the Journal of the American Chemical Society, Vol. 54, 4739 (1932).]

442167

Digitized by the Internet Archive
in 2026

https://archive.org/details/condensationofce0054jsco

THE CONDENSATION OF CERTAIN METHYLKETONES WITH ISATIN BY THE KNOEVENAGEL METHOD

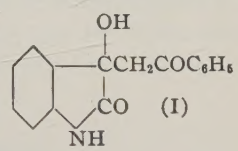
The Pfitzinger[1] method of synthesis of substituted cinchoninic acids, like cinchophen, from isatin and methyl ketones with concentrated potash, serves as a convenient reaction when no alkali-sensitive groups are present. The desirability of a more gentle method suggested the Knoevenagel[2] catalysts in place of the alkali.

When an alcoholic solution of isatin and acetophenone containing a small quantity of diethylamine is allowed to stand overnight a copious yield of a product (I) is obtained. The product is not cinchophen but is, according to its empirical formula, an addition product

$$\underset{\text{Isatin}}{C_8H_5O_2N} + \underset{\text{Acetophenone}}{C_8H_8O} = \underset{\text{(I)}}{C_{16}H_{13}O_3N}$$

The same product (I) is obtained by the use of piperidine or low concentrations of potash. Furthermore, repetition of the procedure described in German Patent 301,591, using cold dilute ammonia, yields (I) ($C_{16}H_{13}O_3N$) again, proving it to be identical with the product described in that patent.[3]

The product is evidently the result of interaction of the beta carbonyl of isatin with the methyl group of acetophenone and its structure is 3-hydroxy-3-phenacyloxindole (I). This structure is postulated on the basis of the following facts. (1) Linkage of acetophenone to the nitrogen of isatin is not a possibility since N-methylisatin also condenses, like isatin, to yield a product with similar chemical properties. (2) Linkage to the alpha carbonyl is decidedly unusual in isatin condensations. Furthermore, isatin-β-anil and isatin-β-bispiperidyl give no product with these catalysts and methods, indicating that the α-carbonyl is not involved in this type of condensation. (3) The chemical properties of the compound favor the structure shown above.



(I)

It has proved difficult to obtain a sharp melting point for (I). Heating the compound at its approximate melting point resulted in its decomposition to isatin and acetophenone, through a reversal of the aldol-like condensation. This behavior is similar to that noted by Kohler and Corson[4]

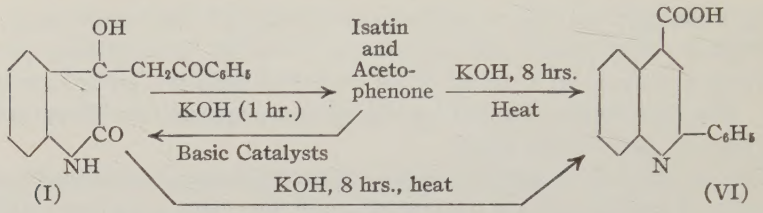
[1] Pfitzinger, *J. prakt. Chem.*, **33**, 100 (1886); **38**, 583 (1888); **56**, 283 (1897).

[2] Knoevenagel, *Ann.*, **281**, 25 (1894); *Ann.*, **288**, 321 (1895); *Ber.*, **31**, 2585, 2596 (1898); *ibid.*, **37**, 4464 (1904).

[3] *Chem. Zentr.*, I, 148 (1918).

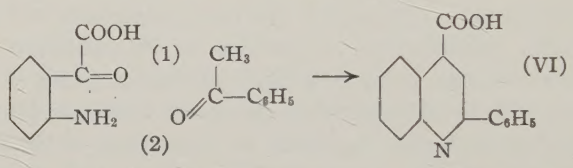
[4] Kohler and Corson, *J. Am. Chem. Soc.*, **45**, 1975 (1923).

for their condensation product of methyl benzoyl formate and methyl cyanoacetate. This same decomposition was noted when the product (I) was treated with potash solution with a short period of warming. Using potash under the more strenuous Pfitzinger conditions resulted in the formation of cinchophen—not, apparently, through any rearrangement of (I), but rather through its decomposition into isatin and acetophenone followed by condensation of these two, after ring opening of the isatin.

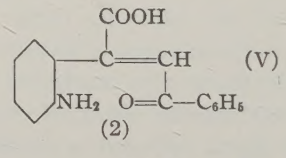


Treatment of the 3-hydroxy-3-phenacyloxindole with acid resulted in its dehydration to yield 3-phenacylideneoxindole (II).

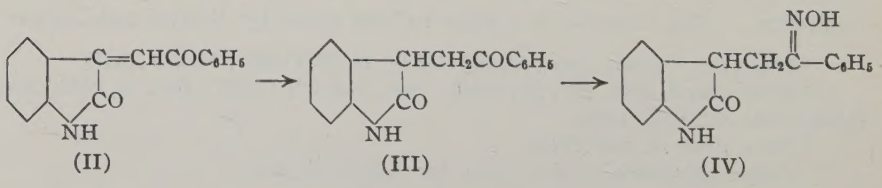
The Pfitzinger reaction for the formation of cinchophen (VI) is ordinarily conceived to take place in the following fashion



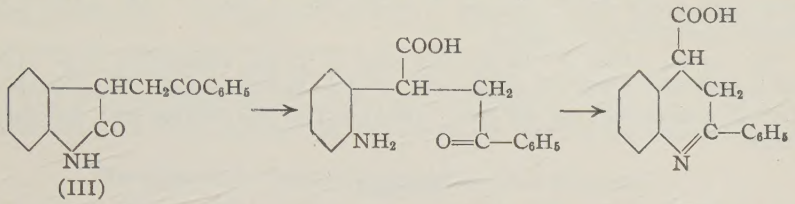
If condensation occurs first at position (1) to yield (V) as an intermediate



it might be assumed that compound (II) would, upon ring opening by hydrolysis with potash also yield (V) and subsequently, through reaction of the groups at (2), yield cinchophen. This assumption is contrary to the experimental result. No cinchophen could be isolated from the hydrolysis reaction mixture. It is possible that (V) is a "trans" isomer and will not form the quinoline derivative for this reason. This point has not yet been investigated.



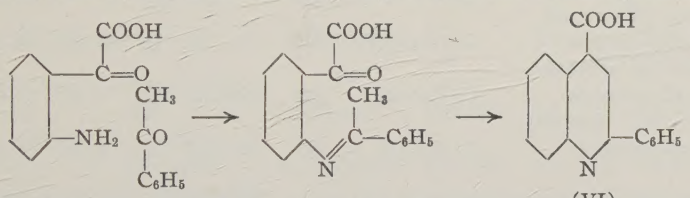
3-Phenacylideneoxindole (II) upon reduction yielded 3-phenacyloxindole (III). Again in this case it might be assumed that treatment with concentrated potash would lead to the following changes



(III)

Compound (III) proved surprisingly stable, being returned unchanged from the concentrated potash solution after several hours of heating. Oxime (IV) formation attested to the ketone structure of (III).

Compound (II) cannot, therefore, be an intermediate in the course of the Pfitzinger synthesis of substituted cinchoninic acids. It would seem probable that the Pfitzinger reaction proceeds through reaction *first* of the ketone carbonyl with the amino group of the *o*-aminobenzoylformic acid.



(VI)

In the case of the products (described in the Experimental Part) formed through the interaction of isatin or N-methylisatin with acetophenone or para-(Br, Cl, CH_3, OCH_3)-substituted acetophenones, the reactions and general properties are completely analogous to those described above.

Experimental Part

3-Hydroxy-3-phenacyloxindole (I) and Derivatives

(A) By the Action of Diethylamine.—Five grams of isatin and an equimolecular amount of acetophenone were dissolved in 100 cc. of absolute alcohol and diethylamine (10 drops) was added. The mixture was allowed to stand overnight at room temperature. The yellow needles which formed were separated by filtration and were recrystallized from alcohol. This procedure was also followed in the reactions of N-methylisatin with acetophenone and of isatin with para-(methoxy, chloro, bromo)-acetophenones (Table I). Piperidine may be substituted for diethylamine, giving comparable yields.

(B) By the Action of Other Catalysts.—Variations of Method "A" were tried in the condensation of isatin and acetophenone, substituting other catalysts for diethylamine. *Ammonia* gave a slightly improved yield of product (72%). The reaction was carried out at room temperature, using 2 cc. of concentrated ammonium hydroxide in 15 cc. of 33% ethyl alcohol per gram of isatin. *Potassium hydroxide* was tried in various amounts. The concentration for the optimum yield (85%) was found to be 15 cc. of 60% ethyl alcohol, containing 0.16% of potash, per gram of isatin.

Decomposition of 3-Hydroxy-3-phenacyloxindole (I) into Isatin and Acetophenone

(A) **By Heat.**—A 2-g. sample of (I) was heated slowly in a bath of sulfuric acid until the melting range of the material was reached. Evident decomposition resulted with a marked odor of acetophenone. Fractional crystallization of the residue yielded a small quantity (0.2 g.) of isatin.

(B) **By the Action of Potash.**—One gram of (I) was dissolved in 10 cc. of 95% ethyl alcohol, and to this was added 10 cc. of 10% alcoholic potash. The mixture was heated on a steam-bath for one hour. Isatin (0.3 g.) was isolated from the reaction mixture.

TABLE I

Products by method "A"	Formula	Yield, %	Corr. m. p., °C.	Analyses	Calcd.	Found	
3-Hydroxy-3-phenacyl-oxindole	$C_{16}H_{13}O_3N$	63	169–172 dec.	C,	71.92	72.33	72.44
				H,	4.87	4.81	4.93
				N,	5.20	5.05	
3-Hydroxy-1-methyl-3-phenacyloxindole	$C_{17}H_{15}O_3N$	72	168–170 dec.	C,	72.6	73.0	
				H,	5.34	5.40	
3-Hydroxy-3(4′-chloro-phenacyl)-oxindole	$C_{16}H_{12}O_3NCl$	87	175–176	Cl,	11.82	11.79	
3-Hydroxy-3(4′-bromo-phenacyl)-oxindole	$C_{16}H_{12}O_3NBr$	87	178–181	Br,	23.09	23.05	
3-Hydroxy-3(4′-methyl-phenacyl)-oxindole	$C_{17}H_{15}O_3N$	85	185–186	N,	4.98	4.90	
3-Hydroxy-3-(4′-methoxy-phenacyl)-oxindole	$C_{17}H_{15}O_4N$	86	186–187	N,	4.71	4.67	

Cinchophen (2-Phenylquinoline-4-acid) from 3-Hydroxy-3-phenacyloxindole (I).—A 5-g. sample of (I) was dissolved in 24 cc. of 95% alcohol and 33% potash solution (12 cc.) was added. The mixture was heated on a steam-bath for eight hours. Acidification resulted in the precipitation of a white solid which was recrystallized from alcohol. Cinchophen (60% yield) was identified by its melting point and a mixed melting point with a commercial sample.

TABLE II

Dehydrating agent plus: -oxindole	Product, -oxindole	Formula	M. p., °C. (corr.)	Yield, %	Analyses	Calcd.	Found
3-Hydroxy-3-phenacyl-	3-Phenacylidene-	$C_{16}H_{11}O_2N$	193–194	92	C,	77.10	76.74
					H,	4.42	4.39
					N,	5.61	5.50
3-Hydroxy-1-methyl-3-phenacyl-	1-Methyl-3-phenacylidene-	$C_{17}H_{13}O_2N$	127–128	76	C,	77.55	77.70
					H,	4.94	4.96
3-Hydroxy-3-(4′-chlorophenacyl)-	3-(4′-Chlorophen-acylidene)-	$C_{16}H_{10}O_2NCl$	209–210	95	Cl,	12.52	12.65
3-Hydroxy-3-(4′-bromophenacyl)-	3-(4′-Bromophen-acylidene)-	$C_{16}H_{10}O_2NBr$	218–219	85	Br,	24.35	24.06
3-Hydroxy-3-(4′-methylphenacyl)-	3-(4′-Methyl-phenacylidene)-	$C_{17}H_{13}O_2N$	182–183	85	N,	5.32	5.30
3-Hydroxy-3-(4′-methoxyphen-acyl)-	3-(4′-Methoxy-phenacylidene)-	$C_{17}H_{13}O_3N$	201	89	N,	5.01	4.95

Dehydration of 3-Hydroxy-3-phenacyloxindole (I) and Derivatives

(A) By Aqueous Alcoholic Hydrochloric Acid.—A mixture containing 8 g. of (I), 25 cc. of alcohol and 50 cc. of concd. hydrochloric acid (or 50 cc. of 20% sulfuric acid) was allowed to stand overnight (or was heated for one-half hour at 100°). Fine orange-red needles formed. The product was recrystallized from ethyl alcohol. This procedure was also used in the case of certain derivatives of (I) (Table II).

(B) By Hydrochloric Acid in Acetic Acid.—When a mixture containing 2 g. of (I), 0.5 cc. of concd. hydrochloric acid and 20 cc. of glacial acetic acid, was warmed on the steam-bath for fifteen minutes and then cooled, the same product formed as in "A."

Reduction of 3-Phenacylideneoxindole and Derivatives

By Sodium Hydrosulfite.—3-Phenacylideneoxindole (5 g.) was partially dissolved in 75 cc. of 95% ethyl alcohol. To this was added 5 g. of sodium hyposulfite ($Na_2S_2O_4$) dissolved in 25 cc. of water. At room temperature, reduction was complete in about two hours; at steam-bath temperature, in twenty minutes. Upon thorough cooling of this solution, white crystals were formed. The product was purified by recrystallization from ethyl alcohol (Table III).

TABLE III

$Na_2S_2O_4$ plus: -oxindole	Product, -oxindole	Formula	M. p., °C. (corr.)	Yield, %	Analyses	Calcd.	Found
3-Phenacylidene-	3-Phenacyl-	$C_{16}H_{13}O_2N$	177	89	C,	76.51	76.30
					H,	5.18	5.13
1-Methyl-3-phen-acylidene-	1-Methyl-3-phen-acyl-	$C_{17}H_{15}O_2N$	134–135	65	N,	5.20	5.28
3-(4′-Chlorophen-acylidene)-	3-(4′-Chloro-phenacyl)-	$C_{16}H_{12}O_2NCl$	182–183	84	Cl,	12.44	12.47
3-(4′-Bromophen-acylidene)-	3-(4′-Bromophen-acyl)-	$C_{16}H_{12}O_2NBr$	191–192	90	Br,	24.21	24.19
3-(4′-Methyl-phenacylidene)-	3-(4′-Methyl-phenacyl)-	$C_{17}H_{15}O_2N$	145–146	78	N,	5.28	5.24
3-(4′-Methoxy-phenacylidene)-	3-(4′-Methoxy-phenacyl)-	$C_{17}H_{15}O_3N$	164–165	76	N,	4.98	4.92

3-Phenacyloxindole Oxime.—3-Phenacyloxindole (5 g.) was dissolved in 100 cc. of 95% ethyl alcohol and to this was added an aqueous solution of hydroxylamine, prepared by adding 12.5 cc. of 10% sodium hydroxide to 2.5 g. of hydroxylamine hydrochloride in 10 cc. of water. The mixture was heated on a steam-bath for one hour and on cooling the oxime crystallized from solution. It was recrystallized from ethyl alcohol; yield 85%, m. p. 198–199°.

Anal. Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.18; H, 5.26. Found: C, 71.95; H, 5.22.

Attempted Rearrangement of 3-Phenacylideneoxindole to Cinchophen.—A mixture of 3-phenacylideneoxindole (2.7 g.) in 12 cc. of ethyl alcohol and 6 cc. of 33% potash was refluxed for three hours. The mixture was cooled and acidified with hydrochloric acid. A dark brown gummy material separated which solidified upon standing under water. No cinchophen could be obtained from this mass.

Attempted Rearrangement of 3-Phenacyloxindole to 3,4-Dihydro-2-phenylcinchoninic Acid.—3-Phenacyloxindole (5 g.) was treated with the concentrations of water, alcohol and potash mentioned directly above. The mixture was refluxed for fifteen hours, then cooled and acidified. The product (4 g.), after purification, was found to be unchanged 3-phenacyloxindole.

Summary

Isatin has been condensed with acetophenone to yield 3-hydroxy-3-phenacyloxindole. Some chemical properties and derivatives of this compound are described.

3-Phenacylideneoxindole and 3-phenacyloxindole failed to rearrange to give quinoline derivatives under the experimental conditions employed. This suggested that 3-phenacylideneoxindole is not an intermediate in the Pfitzinger synthesis of cinchophen from isatin and acetophenone.